HEALTH EFFECTS INSTITUTE

Extended Analysis of the American Cancer Society Study of Particulate Air Pollution and Mortality

INTRODUCTION

The American Cancer Society (ACS) Cancer Prevention Study II (CPS-II), a large ongoing prospective study of mortality in adults initiated in 1982, was one of two U.S. cohort studies central to the 1997 debate on the National Ambient Air Quality Standard (NAAQS) for fine particulate air pollution in the United States. Because of the high importance of the original ACS study in formulating regulations and the controversy generated by the limitations of that study, the U.S. Environmental Protection Agency (U.S. EPA), the Congress, and industry requested that the Health Effects Institute conduct the Particle Epidemiology Reanalysis Project with the objective of independently and rigorously assessing the original data and findings. The results of the Reanalysis Project validated the quality of the original data (which included 7 years of follow-up), replicated the original results, and tested those results against alternative risk models and analytic approaches.

After the Reanalysis Project, Dr. Arden Pope and colleagues undertook an Updated Analysis of the ACS cohort using an additional 10 years of follow-up and exposure data. Recent advances in statistical modeling were incorporated into these analyses.

As described in Research Report 140, Dr. Daniel Krewski and colleagues, with HEI's support, conducted an Extended Analysis of the same cohort. This research increases the follow-up period for the ACS cohort to 18 years (1982 to 2000) — 11 years more than the original study. The investigators have produced national estimates of the risks of death from various causes and have extended the range of analyses to include refinements of statistical methods and incorporate sophisticated control of bias and confounding.

SUMMARY

The cohort for the current study consists of approximately 360,000 participants residing in areas of the country that have adequate monitoring information on levels of particulate matter with an aerodynamic diameter of 2.5 µm or smaller ($PM_{2.5}$) for 1980 and about 500,000 participants in areas with adequate information for 2000. The causes of death obtained from death certificates during follow-up that were analyzed included all causes, cardiopulmonary disease (CPD), ischemic heart disease (IHD, reduction of blood supply to the heart, potentially leading to heart attack), lung cancer, and all other causes. Data for 44 personal, individual-level covariates, based on participants' answers to a 1982 enrollment questionnaire, were also used for the analyses. Dr. Krewski's research team also collected data for seven ecologic (neighborhood-level) covariates, each of which represents local factors known or suspected to influence mortality, such as poverty level, level of education, and unemployment (at both Zip Code and city levels).

Long-term average exposure variables were constructed for $PM_{2.5}$ from monitoring data for two periods: 1979–1983 and 1999–2000. Similar variables were constructed for long-term exposure to other pollutants of interest from single-year (1980) averages, including total suspended particles, ozone (O_3), nitrogen dioxide, and sulfur dioxide (SO_2). Exposure was averaged for all monitors within a metropolitan statistical area (MSA) and assigned to participants according to their Zip Code area (ZCA) of residence.

Dr. Krewski's team chose the standard Cox proportional-hazards model (and a variation to allow for random effects) to calculate hazard ratios for various cause-of-death categories associated with

the levels of air pollution exposure in the cohort. They extended the random effects Cox model to accommodate two levels of information for clustering and for ecologic covariates. Three main analyses were conducted: a Nationwide Analysis, Intra-Urban Analyses in the New York City (NYC) and Los Angeles (LA) regions, and an analysis designed to investigate whether critical time windows of exposure to pollutants might have affected mortality in the cohort.

Nationwide Analysis

For the Nationwide Analysis using the standard Cox model, the associations between average $PM_{2.5}$ concentrations in both 1979–1983 and 1999–2000 and mortality from all causes (except the category of "all other causes") were statistically significant. The hazard ratio (HR) for death was elevated by 3% to 15%, depending on the cause of death, for each increase of 10 μg/m³ in $PM_{2.5}$. When the random effects Cox model was used with added control for ecologic covariates, the effect estimates increased slightly and remained significant; the strongest estimate was for IHD (HR = 1.24; 95% confidence interval [CI], 1.19–1.29). These effect estimates were, in general, higher than those found in some previous analyses of this cohort. The association of mortality with summer O_3 levels (calculated from concentrations measured from April to September 1980) was small, but significant, for deaths from all causes (HR = 1.02; 95% CI, 1.01–1.03) and from CPD (HR = 1.03; 95% CI, 1.02–1.04).

In earlier analyses of this cohort, investigators found that increasing education levels appeared to reduce the effect of $PM_{2.5}$ exposure on mortality. Results from the current study show a similar pattern, although with somewhat less certainty, for all causes of death except IHD, for which the pattern was reversed.

Intra-Urban Analyses

For the NYC Analysis, land-use regression (LUR) models were created to estimate exposure to $PM_{2.5}$ using concentrations averaged over 3 years or over the winter months only for 1 year. Annual average concentrations were calculated for each of 62 monitors from 3 years of daily monitoring data for 1999 through 2001. Those data were combined with land-use data collected from traffic-counting systems, roadway network maps, satellite photos of the study area, and local government planning and tax-assessment maps to assign estimated exposures to the ACS participants. As

with the Nationwide Analysis, the team used the random effects Cox model to calculate HRs and incorporated the 44 individual-level covariates as well as the 7 ecologic covariates at the ZCA and MSA scales.

In the LA Analysis, the investigators used both LUR and kriging (a method of interpolating missing values) to estimate exposure concentrations for cohort members. The Cox models used to calculate associations between exposure and mortality included the same individual-level and ecologic covariates as in the NYC Analysis. The LA Analysis reported results separately for analyses that used exposure based on LUR and those based on kriging of monitored concentrations. The investigators assembled data from several sources for the LUR models, including the California EPA's 23 $PM_{2.5}$ monitors and the California Air Resources Board's database for 42 sites monitoring O_3.

Despite the common methodologic basis for the NYC and LA Analyses, the resulting LUR exposure models and associations between exposure and mortality were strikingly dissimilar. The LA results show much larger HRs than the NYC results, except for mortality due to IHD (LA: HR = 1.33; 95% CI, 1.08–1.63; NYC: HR = 1.47; 95% CI, 1.00–2.00; both per 10-μg/m³ increase in $PM_{2.5}$). These differences may arise from the range of exposures derived for cohort members residing in each area, the relative uniformity of $PM_{2.5}$ exposure in the NYC region, and the differences between the land-use variables selected as the most appropriate for inclusion in the LUR models that were constructed for the two metropolitan areas.

Critical Periods of Exposure Analysis

Dr. Krewski's team performed an analysis designed to explore whether more recent exposures to air pollution are more or less strongly associated with mortality than exposures further in the past. Exposure profiles for this analysis were constructed from average $PM_{2.5}$ and SO_2 concentrations for periods 1 to 5 years, 6 to 10 years, and 11 to 15 years before death. As with other analyses, the investigators used the standard Cox model including individual-level covariates.

The investigators considered the time window with the best-fitting model (judged by the lowest Akaike information criterion [AIC] statistic, which is a measure of how well a model fits the available data) to be the period during which pollution had the strongest influence on mortality. Overall, differences in model fit, HRs, and CIs among the three 5-year exposure periods were small and demonstrated no definitive patterns.

High correlations between exposure levels in the three periods may have reduced the ability of this analysis to detect any differences in the relative importance of the time windows.

DISCUSSION

The basic Cox proportional-hazards model used for the mortality analyses has two major limitations that the investigators addressed in innovative ways developed specifically for this study: confounding by ecologic factors and spatial autocorrelation. Ecologic confounders are risk factors for mortality that are observed at the neighborhood level, rather than the individual level. In the current study, in contrast to the Reanalysis Project, ecologic information was collected at the ZCA level as well as the MSA level, although not all ecologic covariates considered previously were included in this analysis. Spatial autocorrelation arises from the way values for certain variables tend to be similar for people (or areas) that are geographically close. For example, people who live in the same household or neighborhood — or even in similar neighborhoods in the same city — tend to have similar health risks (diet, smoking habits, access to health care), as well as similar proximity to sources of exposure (e.g., freeways and industrial areas). The spatial models in this analysis differed from those used in the Reanalysis by including random effects at the ZCA, city, and state levels and by adjusting for correlation between adjacent ZCAs, cities, and states.

In its evaluation of the study by Krewski and colleagues, the Review Committee agreed with the investigators that key results were robust when adjusted for ecologic covariates and spatial autocorrelation in the statistical models. In a recently published follow-on study of O_3 and respiratory outcomes in the ACS data, including the same individual and ecologic covariates as the current study, Dr. Michael Jerrett and associates found no indication of important residual spatial autocorrelation in the association between O_3 and mortality.

Because the Reanalysis Project tested extensively for confounding by gaseous pollutants of the relationship between fine particles and mortality, the Krewski team instead focused the current study on an extensive exploration of spatial autocorrelation in a series of one-pollutant models. The Committee thought that the inclusion of some two-pollutant analyses would have strengthened the study. The authors note, however, that the available data for most gaseous pollutants were not sufficient for such analyses, since they came from only a few locations in each city and could not adequately represent the high degree of spatial variability of pollutant levels in a given metropolitan area.

The present report combines deaths from cardiovascular and respiratory causes—a decision that is important for continuity with earlier studies but one that makes the results more difficult to interpret biomedically. The report singled out the associations between $PM_{2.5}$ and IHD, consistent with previous investigations with this cohort, but the Committee felt it would be useful in the future to see the results for other categories of cardiovascular disease, such as stroke and heart failure, presented alongside those for IHD.

The fundamental difference in exposure between the two Intra-Urban Analyses lies in the different relative influence of regional background concentrations of $PM_{2.5}$. The intra-urban studies primarily investigated variability in local exposure within the regions that was driven by local sources such as traffic, industry, and residential or commercial emissions. Despite the substantial differences in how the LUR models were constructed and the likely quality of the data used, the LUR models for LA and NYC were both successful in explaining a moderate percentage of variability (60 to 65%) in $PM_{2.5}$ concentrations measured at the monitoring sites. The range of average annual monitored $PM_{2.5}$ concentrations considered in developing the models was not very different between LA (9.5 to 28 $\mu g/m^3$) and NYC (10 to 20 $\mu g/m^3$). However, the resulting ranges of exposure assigned by the LUR models in LA (< 10 to >125 $\mu g/m^3$) and NYC (8 to 20 $\mu g/m^3$), by comparison, suggest that levels of $PM_{2.5}$ are regionally determined in NYC and highly locally variable in LA.

The intra-urban results for the two regions were very different, with a strong positive and significant association between $PM_{2.5}$ exposure and mortality from CPD in LA and no significant association in NYC. Both the LA and NYC results showed significant associations between $PM_{2.5}$ and mortality from IHD, consistent with the results of the Nationwide Analysis. The authors note that differences in the estimated HRs for LA and NYC were partially attributable to the different — and opposite — ways that mortality that was not explained by the individual and ecologic variables in the Cox models was distributed relative to the varying $PM_{2.5}$ exposure levels in the two cities. The higher exposures in LA tended to occur in areas characterized by low socioeconomic status (and relatively high expected mortality), whereas the higher exposures in NYC were generally found in areas of high socioeconomic status (and relatively low expected mortality).

The Committee noted that the inconclusive results from the NYC Analysis (aside from that for IHD) were probably due to too little variation in $PM_{2.5}$ exposure across the NYC area, owing to the regional nature of $PM_{2.5}$ exposure in the Northeastern United States. Relatively uniform exposures would reduce the ability of the statistical models to detect patterns of mortality relative to exposure and to estimate HRs with precision. As for the LA results, the authors believe that the higher estimates are due to reduced error in the assignment of exposures. However, the Committee saw no persuasive argument that exposure measurement error would be expected to be less in the LA or NYC studies than in the Nationwide Analysis. Therefore, the Committee believes that the most likely explanation for the largely null results for the NYC Analysis and their divergence from the LA and Nationwide results was the low variability in $PM_{2.5}$ exposure levels across the NYC region.

The epidemiologic design used in the analysis of Critical Periods of Exposure was more complex than that of the full Nationwide Analysis because it used two distinct subcohorts of subjects from the main ACS cohort, rather than the whole cohort as in the Nationwide Analysis. For each deceased ACS participant in each subcohort, time windows of exposure were calculated as average exposures during successive five-year periods preceding the date of death.

The use of AIC to compare models including different five-year windows of past exposure is broadly reasonable, since the number of variables in each model being compared was the same. The Committee was somewhat disappointed that the investigators did not present results for "multi-window" models, in which the effects of exposure in one time window are controlled for the effects of exposure in another time window. Although it is important to know whether more recent exposure has a greater effect on risk than earlier exposure, the Committee considered that the evidence presented was not substantial enough to draw conclusions based on the extremely small differences in AIC values resulting from exchanging exposure in one time window with another.

CONCLUSIONS

The Extended Analysis represents a broadly sound and thorough analysis of an already important cohort study, with several innovative features. The results consolidate earlier findings by show-ing that the application of state-of-the-art statistical approaches to controlling confounders and spatial autocorrelation does not materially change risk estimates; important residual confounding (by climate and possibly other unmeasured determinants of large-scale spatial variation) cannot be excluded, however, particularly in the Nationwide Analysis. In analyzing the extended follow-up data from the ACS cohort for mortality, the report also provides new risk estimates, including — for the first time — an estimate for O_3 and premature mortality.

The Intra-Urban Analysis for LA suggests that mortality risks associated with $PM_{2.5}$ exposure may be elevated when there is a strong local component of exposure. When the NYC and LA Analyses are taken together, however, they underscore the important point that cities differ markedly in their local exposure conditions and emphasize the variable importance of the contributions of local sources to the overall risk of mortality associated with $PM_{2.5}$ exposure. These divergent results argue for caution in extrapolating from such studies in any one metropolitan area to other areas.

No single study can be the basis for accepting the existence of a causal relationship between air pollution and mortality. With this in mind, the Committee thought that — with the emergence of new cohort evidence from the United States and Europe — the similarities and differences among the results of the various studies need to be examined closely. Nevertheless, the size and character of the ACS cohort makes it likely that it will remain preeminent.